suspension of lithium aluminum hydride (1.2 g.) in ether (240 ml.), and the mixture was stirred at room temperature for 1 hr. Water (30 ml.) was added dropwise and the solvent was decanted. The residue was washed thoroughly with hot chloroform. The combined solvents were evaporated, and the product VIIb was obtained as needles (449 mg.), m.p. 227–230° by crystallization from acetone–petroleum ether. The analytical sample of the same melting point had $[\alpha]_D^{25}$ + 103° (methanol:chloroform 1:1); λ_{max} 221 (ϵ 9740), 278 (ϵ 1940), and 286 mμ (ϵ 1880); ν_{max} 3497, 1612, 1580, 1504, and 1048 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{32}O_7$ (420.49): C, 65.69; H, 7.67. Found: C, 65.57; H, 8.00.

16α-Hydroxy-19-norhydrocortisone (IX). Lithium wire (300 mg.) was added in small pieces to a stirred solution of 20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-triene-11β,16α,17α,21-tetrol (VIIb, 300 mg.) in liquid ammonia (90 ml.), dioxane (10 ml.), and ethanol (4.5 ml.). The blue coloration disappeared in about 15 min., and the mixture was allowed to evaporate. Water was added and the mixture was extracted with methylene chloride. The extract was washed with water and dried. Evaporation of solvent followed by crystallization of the residue from methanol–ethyl acetate gave 20-ethylenedioxy-3-methoxy-19-norpregna-2,5(10)-diene-11β,16α,17α,21-tetrol (VIII, 210 mg.) as needles, m.p. 210–225°. This compound (VIII, 200 mg.), methanol (20 ml.), and dilute sulfuric acid (2 ml.; 8% v./v.) were heated on the steam bath for 1 hr. Ethyl acetate (100 ml.) was added to the cooled solution, and the mixture was washed with aqueous sodium bicarbonate solution, water, and dried. Removal of solvent and crystallization of the residue from methanol–ethyl acetate gave 16α-hydroxy-19-norhydrocortisone as small prisms (100 mg.), m.p. 228–231° dec. The analytical sample had m.p. 229–232° dec.; $[\alpha]_D^{25}$ + 63.5° (pyridine); λ_{max} 241 mμ (ϵ 17,800); ν_{max} 3401, 1709, 1661, and 1621 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{28}O_6$ (364.42): C, 65.91; H, 7.74. Found: C, 65.84; H, 7.95.

11β,21-Dihydroxy-16α,17α-isopropylidenedioxy-19-norpregn-4-ene-3,20-dione (X). Perchloric acid (1 drop; 72%) was added to a stirred suspension of 16α-hydroxy-19-norhydrocortisone (50 mg.) in acetone (5 ml.). After 2 hr., the solution was diluted with water, and the mixture was extracted with methylene chloride. The extract was washed with aqueous sodium bicarbonate solution, water, and dried. Removal of solvent gave the acetonide X which crystallized as needles (50 mg.), m.p. 209–213°, from acetone–petroleum ether. Further crystallization gave m.p. 218–224°; $[\alpha]_D^{25}$ +133°; λ_{max} 240 mμ (ϵ 18,300); ν_{max} 3484, 1718, 1664, and 1626 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.97. Found: C, 68.53; H, 8.15.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, A DIVISION OF AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. XX.[1] Some Transformations of 16β,21-Diacetoxy-17α-hydroxypregn-4-ene-3,20-dione

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Alkaline treatment of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia) yielded 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) and two isomeric by-products tentatively formulated as 16α,17α-dihydroxy-17β-hydroxymethyl-D-homoandrost-4-ene-3,17a-dione (IIIa) and 16α,17aα-dihydroxy-17aβ-hydroxymethyl-D-homoandrost-4-ene-3,17-dione (IVa). Acidic treatment of Ia afforded 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib) and its C-16 monoacetate (Ic).

In view of the importance of the biological and therapeutic properties of 9α-halo-16α-hydroxycorticoids,[2] it would appear to be of considerable interest to prepare 16β-oxygenated isomers of some of these active compounds. For a thorough study of this type of compound it was desirable to study the chemistry of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia).[3,4]

Treatment of the diacetate Ia under a variety of alkaline conditions[4] (potassium hydroxide, sodium methoxide, sodium carbonate, or sodium bicarbonate) gave in all cases an easily isolated solid which proved to be 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa).[5,6]

Careful partition chromatography of some of the above experiments has provided at least two more products which are isomeric with IIa and are discussed below.

The same type of retroaldol mechanism employed by Wendler and co-workers[7] to elucidate the D-homoannulation of a 16,17α-dihydroxy-20-keto steroid may be utilized to explain the epimerization at the C-16 position. Thus, a retroaldol ring opening followed by closure, as illustrated by partial structures A, B, and C, is a plausible mechanism.[8,9]

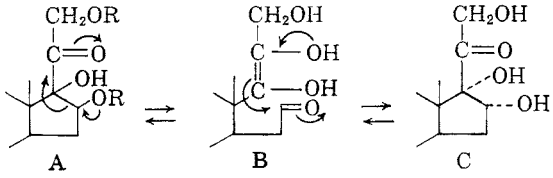
The preference for a 16α-hydroxyl conformation in

(1) Paper XIX, J. J., Brown and S. Bernstein, *J. Org. Chem.*, **26**, 5033 (1961).

(2) (a) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **81**, 1689 (1959); (b) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 1696 (1959); (c) S. Bernstein, *Recent Progress in Hormone Research*, **14**, 1 (1958); (d) R. H. Freyberg, C. A. Berntsen, Jr., and L. Hellman, *Arthritis and Rheumatism*, **1**, 215 (1958); (e) J. S. Mills, A. Bowers, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 3399 (1960); (f) S. Bernstein, M. Heller, F. J. McEvoy, and S. M. Stolar, *J. Org. Chem.*, **26**, 505 (1961).

(3) For a preliminary communication concerning some of this work see S. Bernstein, M. Heller, and S. M. Stolar, *J. Am. Chem. Soc.*, **81**, 1256 (1959).

(4) K. Heusler and A. Wettstein, *Chem. Ber.*, **81**, 1301 (1954).



the final product is probably influenced by the reduction of nonbonded interference of the C-18 methyl group with a C-16 hydroxyl group in the α-configuration. Also, there is a possibility that hydrogen bonding in a 16α,17α-diol exerts an influence which favors the designated final product.

The considerable number of reports published in the last few years on D-homo formation of 16,17-dihydroxy-20-keto steroids,[4,7,10] leads one to consider that the unknown compounds mentioned above were also D-homo isomers of IIa. Especially from the work of Wendler and Taub[10b,c] one may suggest as a tentative assignment for the major isomer the structure 16α,17α - dihydroxy - 17β-hydroxymethyl - D - homoandrost - 4 - ene - 3,17a-dione (IIIa) while the minor isomer would have the structure 16α,17aα - dihydroxy - 17aβ - hydroxymethyl - D - homoandrost - 4 - ene - 3,17 - dione (IVa). Both of these compounds readily form diacetates (IIIb and IVb) and acetonides (Va and VI).

There are certain physical data to support these formulations. Proton nuclear magnetic spectra[11] of the diacetate IIIb revealed a methyl proton shift of 317 c.p.s. associated with the C-18 methyl group. Similarly, the diacetate IVb had a methyl proton shift of 317 c.p.s. associated with the C-18 methyl group. The proton shift of the C-18 methyl group of 16α,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (IIb)[6,12] was at 339 c.p.s. This type of proton shift was also observed in comparing the C-18 methyl frequency of 17β-hydroxymethyl-16α,-17α - isopropylidenedioxy - D - homoandrost - 4-ene-3,17a dione (Va) at 324 c.p.s. and of 17aβ-hydroxymethyl - 16α,17aα - isopropylidenedioxy-D-homoandrost - 4 - ene - 3,17 - dione (VI) at 323 c.p.s. with that of 21-hydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (VII) at 347 c.p.s. Previous empirical findings[10f,13] indicated that a shift of *ca.* −20 to −25 c.p.s. (60 mc.) occurred when the environment of an angular methyl group was changed from the juncture of one five-membered ring and one six-membered ring to that of two six-membered rings. In the case of the two D-homo diacetates (IIIb and IVb) when compared to the normal diacetate (IIb) the shift was −22 c.p.s. The shift for the D-homo acetonides (Va and VI) when compared to the normal acetonide VII was 23–24 c.p.s. The best explanation for the data is to assume D-homo formulations for IIIa and IVa.

A further decision as to the assignment of a 17-one or 17a-one structure to the isomers was made through the use of the infrared spectra of the diacetates (IIIb and IVb). The infrared spectrum of the 17-keto diacetate IVb when compared to that of the 17-keto-triol IVa revealed a definite vicinal interaction between the saturated carbonyl function (1722 cm.$^{-1}$) and an acetate group (1750 cm.$^{-1}$) of IVb while the absorption of the saturated carbonyl function of the free triol IVa was at 1707 cm.$^{-1}$ Such vicinal interactions require that an acetylated hydroxyl group be adjacent to the

(5) The compound isolated by Heusler and Wettstein[4] from the identical experiment and assumed to be a D-homo compound based on more substantive work with C-21-deoxy steroids was actually IIa. We wish to thank Dr. Wettstein for sending us a sample of his compound for direct comparison.

It is also of interest to note that J. Romo and A. R. De Vivar [*J. Org. Chem.*, **21**, 902 (1956)] upon treatment of 21 - acetoxypregn - 4,16 - diene - 3,20 - dione with osmium tetroxide followed by a sodium sulfite–alcohol work-up assumed the product to be a D-homo compound by a comparison with the Wettstein sample. The product proved to be IIa upon direct comparison. We thank Dr. Romo for sending us some of his sample. This again verifies the greater stability of a 20-keto-16α,17α,21-triol to D-homo-annulation conditions when compared to the analogous C-21-deoxy steroid.

(6) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(7) H. Kuo, D. Taub, and N. L. Wendler, *Chem. & Ind.*, 1129 (1959); N. L. Wendler, D. Taub, and H. Kuo, *J. Am. Chem. Soc.*, **82**, 5701 (1960).

(8) The possibility of a retroaldol mechanism for this rearrangement, especially in view of the lack of evidence for a Walden inversion (*vide infra*) was considered prior to Wendler's disclosure.[7] We wish to thank Dr. E. F. Ullman of the Stamford Laboratories, American Cyanamid Co., for a helpful and constructive discussion regarding this mechanism.

(9) H. L. Herzog, M. J. Gentles, A. Mitchell, E. B. Hershberg, and L. Mandell, *J. Am. Chem. Soc.*, **81**, 6478 (1959), have utilized a similar retroaldol mechanism with opening and closing of the D-ring to explain a double bond isomerization in their compounds.

(10) (a) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4377 (1955); (b) N. L. Wendler and D. Taub, *Chem. & Ind.*, 1237 (1957); (c) N. L. Wendler and D. Taub, *J. Am. Chem. Soc.*, **82**, 2836 (1960); (d) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4956 (1959); (e) G. R. Allen, Jr., and M. J. Weiss, *J. Am. Chem. Soc.*, **81**, 4968 (1959); (f) L. L. Smith, M. Marx, J. J. Gabarini, T. Foell, V. E. Origoni, and J. J. Goodman, *J. Am. Chem. Soc.*, **82**, 4616 (1960).

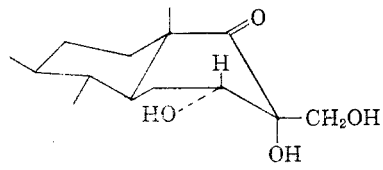
(11) Proton NMR spectra were obtained in deuterochloroform solutions of the samples using a 60 mc. instrument with an internal reference sample of tetramethylsilane. The tetramethylsilane signal was at 385 ± 1 c.p.s. from the external reference standard benzene. All chemical shifts have been converted to the benzene reference. The data and interpretations were kindly provided by L. Johnson and Dr. J. N. Shoolery of Varian Associates, Palo Alto, Calif.

(12) B. Ellis, F. Hartley, V. Petrow, and D. Wedlake, *J. Chem. Soc.*, 4383 (1955).

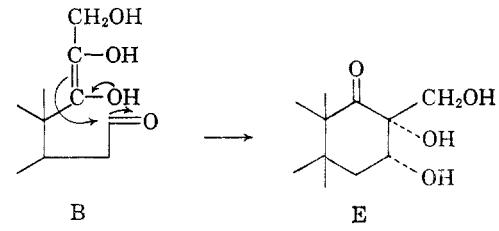
(13) (a) "*NMR*" *at Work*, No. 51, Varian Associates Instrument Division, *Chem. & Eng. News*, Sept. 22, 1958, p. 59; (b) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

saturated carbonyl function.[14] This, obviously, could be achieved by a 16-acetoxy-17-ketone structure such as IVb. Conversely, the lack of interaction exhibited in the infrared spectrum of the diacetate IIIb suggested a 17a-ketone structure as shown.

The previously cited work by Wendler[10b,c] leads one analogously to assign the 16α,17α-diol configurations for the hydroxyl functions that are available for acetonide formation in the 17α-ketone IIIa. The proton nuclear magnetic resonance spectrum of the 17a-keto diacetate IIIb further revealed that the proton at C-16 formed a four-line pattern about 97 c.p.s. with a coupling pattern typical of a large axial-axial coupling.[15] This fact demonstrated that the C-16 hydrogen is axial. The C-16 proton of the acetonide Va also gave an unresolved pattern suggesting axial-axial coupling in the NMR spectrum. In order to rationalize the simultaneous need for an axial and β-C-16 hydrogen atom on IIIa, the recent work of Wendler[16] which demonstrated that the D-ring in this type of compound was actually in the boat conformation[17] must be considered. Thus a partial structure such as D is suggested for the conformation of the D-ring in IIIa, with the C-16-hydroxyl group *alpha* and equatorial and the C-17 hydroxyl group *alpha* and axial.



The already discussed mechanism[7] leading toward an epimerization also is sufficient to allow for D-homo rearrangement to form a D-homo-17a-ketone. The intermediate B could also close to form the 17a-ketone structure E. In fact, the 16α,17α,21-triol IIa and the D-homo triol IIIa were formed in approximately the same yield.[18] The recyclization



of the intermediate B to E would be expected to occur under thermo- dynamic control, so that the 16α-hydroxyl group should be equatorial as discussed above.

The proton NMR of the 17-keto diacetate IVb also revealed that the proton shift at C-16 at 61 c.p.s. exhibited no large axial-axial coupling and was, therefore, equatorial. In fact, the similarities of this spectrum with that of 16α-acetoxy-17aβ-acetoxymethyl-9α-fluoro-11β,17aα-dihydroxypregn-1,4-diene-3,17-dione[10f] indicated that the D-ring environment was identical in both compounds. Furthermore, analogous to the preparation of the latter compound, treatment of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) with ferric chloride[10f] in hot dimethylformamide afforded IVa. This type of compound could be formed through the type of mechanism suggested by Turner.[19] In such a case the C-16-oxygenated group would be maintained alpha during D-homoannulation and the C-16 hydrogen would be beta and equatorial with ring D in the chair conformation. Thus, the 17-keto acetonide VI is formed from a 1,3-diaxial diol. As mentioned previously[10f] a model of 16β,17aβ-acetonide (boat conformation) showed considerable steric interference.

An attempt was made to provide additional chemical evidence for the 16α,17α-diol structure of IIIa by utilizing the scheme employed by Wendler and Taub[10b,c] in a corresponding C-21 deoxy series. Accordingly, the acetonide Va was acetylated to form Vb and the acetonide grouping removed by hot 66% acetic acid to afford the 17β-acetoxymethyl compound IIIc which was highly solvated and could not be definitively characterized. However, IIIc upon treatment with acetone and perchloric acid readily reformed the acetonide Vb. Reaction of the mono-acetate IIIc with methanesulfonyl chloride in pyridine afforded the noncrystalline mesylate IIId. The latter compound was heated to 115° in acetone solution with sodium iodide to form 17-acetoxymethyl-D-homoandrost-4,16-diene-3,17a-dione (VIII). Unfortunately, we were not able to repeat this preparation on a large scale so that the final osmylation step was never attempted.

(14) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 2820 (1952); R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954); D. H. W. Dickson and J. E. Page, *J. Chem. Soc.*, 447 (1955); M. Okada, D. K. Fukushima, and T. F. Gallagher, *J. Biol. Chem.*, 234, 1688 (1959); L. J. Bellamy and R. L. Williams, *J. Chem. Soc.*, 861 (1957); R. N. Jones and G. Roberts, *Chem. & Ind.*, 1269 (1957). Although all the spectra mentioned in the above papers were done in solution, we have never failed to observe the same phenomenon in potassium bromide spectra.

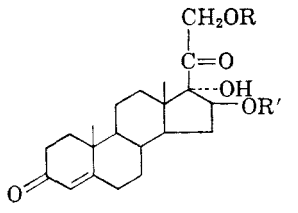
(15) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, 80, 6098 (1958).

(16) N. L. Wendler, *Chem. & Ind.*, 1662 (1958); 20 (1959); *Tetrahedron*, 11, 213 (1960).

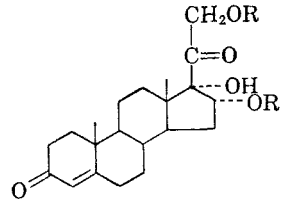
(17) R. S. Rosenfeld, *J. Am. Chem. Soc.*, 79, 5540 (1957) has also given evidence suggesting that a D-homo-17a-ketone possesses a boat conformation while the corresponding D-homo-17-ketone does not.

(18) The already mentioned[5] proclivity for the 16-hydroxy-21-deoxysteroids to D-homoannulate prevents the observation of the epimerization reaction in that series.

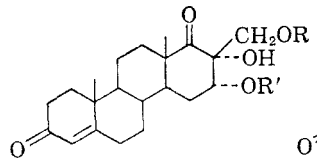
(19) R. B. Turner, *J. Am. Chem. Soc.*, 75, 3484 (1953).



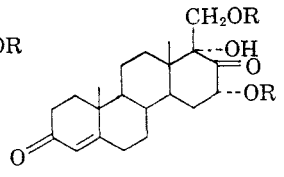
Ia. R = R′ = Ac
b. R = R′ = H
c. R = H; R′ = Ac
d. R = Ac; R′ = OCH



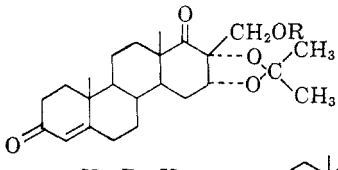
IIa. R = H
b. R = Ac



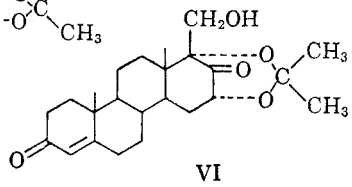
IIIa. R = R′ = H
b. R = R′ = Ac
c. R = Ac; R′ = H
d. R = Ac; R′ = CH_3SO_2



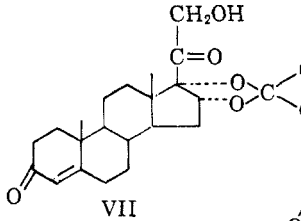
IVa. R = H
b. R = Ac



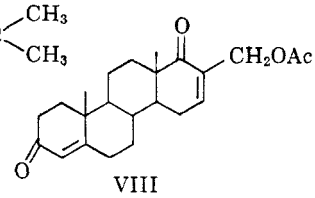
Va. R = H
b. R = Ac



VI



VII



VIII

Beyler and Hoffman[20] have claimed that one hour of bicarbonate treatment of a 17α-hydroxy-16β-formate afforded a 16β,17α-diol. Since prolonged bicarbonate treatment of the 16β,21-diacetate Ia furnished the 16α,17α,21-triol IIa, it was thought desirable to investigate the bicarbonate treatment at the shorter duration of time.

Formic acid–sulfuric acid[20] cleavage of 21-acetoxy-16α,17α-epoxypregn-4-ene-3,20-dione yielded 21-acetoxy-16β-formyloxy-17α-hydroxypregn-4-ene-3,20-dione (Id) which upon treatment for one hour at room temperature with potassium bicarbonate gave 16β-acetoxy-17α,21-dihydroxypregn-4-ene-3,20-dione (Ic) identical with an authentic sample.[20a]

When 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia)[4] was refluxed in methanolic hydrogen chloride, only the D-homo-17a-one (IIIa) was obtained. However, when Ia was treated in methanol with perchloric acid at room temperature, partition chromatography afforded 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib)[21] which was readily reacetylated to the diacetate Ia. Also, there was isolated in the chromatography of the reaction mixture 16β-acetoxy-17α,21-dihydroxypregn-4-ene-3,20-dione (Ic) and an unknown compound isomeric with Ib. The monoacetate Ic was also reacetylated to the diacetate Ia. When the 16β,21-diacetate Ia was treated with methanolic hydrochloric acid at room temperature, essentially the same results occurred as with perchloric acid except that the unknown compound was not isolated.[22] As expected from the above discussion treatment of 16β,17α,21-trihydroxypregn-4-ene-3,-20-dione (Ib) gave in similar fashion to the diacetate Ia the epimeric 16α,17α,21-triol IIa and some D-homo compound IIIa.

Studies done on the ketalization at C-3 of the 16β,21-diacetate Ia and the 16α,21-diacetate (IIa) by the exchange dioxolanation method[24] afforded a surprising difference in results. The only product isolated from the 16β,21-diacetate Ia was the C-3-ketal IX which could be handled in predictable fashion. Accordingly, the latter compound could be reduced with sodium borohydride to furnish the gelatinous diol acetate Xa[25] which was acetylated to 16β,20β,21-triacetoxy-3-ethylenedioxypregn-5-

(20) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(20a) S. Noguchi, *J. Pharm. Soc. (Japan)*, **81**, 385 (1961). It is presumed that migration of the acetate function occurred during the bicarbonate hydrolysis. We wish to thank Dr. Noguchi for a sample of Ic.

(21) Since the completion of this work S. Noguchi, K. Morita, and M. Nishikawa, *Chem. and Pharm. Bull. (Tokyo)*, **8**, 563 (1960) have deacetylated Ia enzymatically to give Ib and also 16β-acetoxy-17α,21-dihydroxypregn-4-ene-3,20-dione (Ic).

(22) The unknown compound and 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIb) and their respective diacetates had the same mobility on various partition and paper chromatographic systems. In fact, both compounds showed identical formation of acetonides and mobilities of these derivatives on a paper chromatographic system.[23] The diacetate of the unknown compound, although it could not be brought to a satisfactory elemental analysis, definitely appeared to have two acetate functions according to its infrared spectrum. Still, comparison of the infrared spectra in solution of the unknown diacetate and the 16α,21-diacetate IIa displayed differences that could only suggest they were indeed different compounds. The unknown compound itself was unaltered by mild basic treatment. An attempt to prepare additional amounts of this unknown compound by relatively large acid hydrolysis of Ia gave none of the desired product. Only the 16β,17α,21-triol Ib, the epimeric 16α,17α,21-triol IIa and the D-homo compounds IIIa and IVa were isolated. In view of this difficulty, work on the unknown product was abandoned.

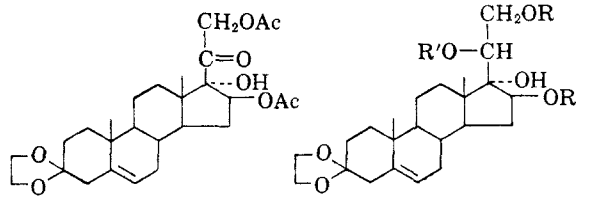
(23) L. L. Smith and T. Foell, *J. Chromatog.*, **3**, 381 (1960). We thank Dr. L. Smith and T. Foell, formerly of the Chemical Process Improvement Department of these laboratories for the results of the paper chromatograms.

(24) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(25) The assignment of the *beta* configuration for the C-20 hydroxyl of compound Xa was presumed from the work of J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955) and D. Taub, R. D. Hofsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 3291 (1959).

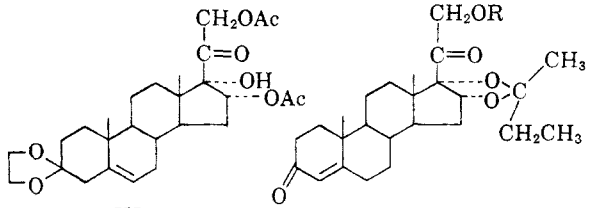
en-17α-ol (Xb). The triacetate Xb was then saponified to the tetrol Xc. Reacetylation of the tetrol Xc then gave the same triacetate Xb. However, treatment of the 3-ketal-16β,21-diacetate IX with base followed by reacetylation formed the epimeric 16α,21 - diacetoxy - 3 - ethylenedioxy - 17α - hydroxypregn-5-ene-20-one (XI) as expected from the work described above. This was an indication that Walden inversion could not explain the epimerization at the C-16 position for saponification of the triacetate Xb to the tetrol Xc did not cause epimerization as shown by the complete reversibility of this reaction.

The exchange dioxolanation procedure on 16α,21-diacetoxy - 17α - hydroxypregn - 4 - ene - 3,20-dione (IIb) did form some of the C-3-ketal XI mentioned above. A considerable quantity of a new compound XIIa which still contained the Δ^4-3-one system was also isolated. Consideration of its infrared spectrum and elemental analysis suggested it was the product of preferential deacetylation at C-16 followed by formation of the 16α,17α-cyclic ketal with methylethylketone under acidic conditions. This was shown to be so by deliberate treatment of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) with methylethylketone and perchloric acid to form 16α,17α-(2′-butylidenedioxy)-21-hydroxypregn-4-ene-3,20-dione (XIIb), which was acetylated to the same compound XIIa mentioned above.



IX

Xa. R = Ac; R′ = H
b. R = R′ = Ac
c. R = R′ = H



XI

XIIa. R = Ac
b. R = H

EXPERIMENTAL

Melting points. All melting points are uncorrected.

Absorption spectra. The ultraviolet spectra were determined in methanol; the infrared spectra were determined in a potassium bromide disk.

Petroleum ether. The fraction used has a b.p. of 60–70°.

16α,17α,21-Trihydroxypregn-4-ene-3,20-dione (IIa); *16α,17α - dihydroxy - 17β - hydroxymethyl - D - homoandrost-4-ene-3,17a-dione* (IIIa); *16α,17aα-dihydroxy-17aβ-hydroxymethyl-D-homoandrost-4-ene-3,17-dione* (IVa). To a solution of 2.5 g. of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia) in 200 ml. of methanol, previously cooled to 0° and flushed with nitrogen, was added a solution of 0.875 g. of potassium hydroxide in 50 ml. of methanol. The reaction mixture was allowed to stand at room temperature for 1 hr., neutralized with acetic acid and evaporated *in vacuo* at 30°. The resulting solid was treated with water, collected by filtration and washed well with water, 1.7 g.; m.p. 185–208°.

Treatment of the solid with boiling methanol (*ca.* 350 ml.) gave an insoluble residue which was filtered to give 380 mg.; m.p. 217–222°. The mother liquor was evaporated to dryness and partitioned on a Celite[26] column using the system 7:1:2—methylene chloride, ethyl acetate, ethylene glycol. Part of hold-back volume 1 and part of 2 were evaporated to give 340 mg.; m.p. 219–223°. Two crystallizations from methanol-ether gave 190 mg.; m.p. 238.5–240.5°. The infrared spectrum was identical to that of an authentic sample of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa). A mixed melting point determination showed no depression.

The latter part of hold-back volume 2 and part of 3 were evaporated to give 530 mg. of solid. Three crystallizations from methanol-ether gave 200 mg. of 16α,17α-dihydroxy-17β - hydroxymethyl - D - homoandrost - 4 - ene - 3,17a-dione (IIIa); m.p. 196–202°; λ_{max} 240 mμ (ε 17,000); ν_{max} 3470, 1712, 1675, 1628 cm.$^{-1}$; $[\alpha]_D^{25}$ +76° (methanol).

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 68.92; H, 8.69.

The original methanol-insoluble fraction isolated above (380 mg., m.p. 217–222°) was crystallized repeatedly from methanol-ether and then from acetone–petroleum ether to give 120 mg. of 16α,17aα-dihydroxy-17aβ-hydroxymethyl-D-homoandrost-4-ene-3,17-dione (IVa); m.p. 227.5–229.5°; λ_{max} 240 mμ (ε 17,000); ν_{max} 3450, 1707, 1670, 1620 cm.$^{-1}$; $[\alpha]_D^{25}$ +80° (methanol).

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 69.51; H, 8.43.

16α-Acetoxy-17β-acetoxymethyl-17α-hydroxy-D-homoandrost-4-ene-3,17a-dione (IIIb). To a solution of 330 mg. of the D-homo triol IIIa in 7 ml. of pyridine, was added 1 ml. of acetic anhydride and the reaction mixture was allowed to stand for 17 hr. at room temperature. Addition of water gave a solid which was collected by filtration and washed well with water; 100 mg., m.p. 240–246°. Two crystallizations from acetone-petroleum ether gave 80 mg. of IIIb, m.p. 244–247°; λ_{max} 238 mμ (ε 17,900); ν_{max} 3510, 1748, 1713, 1680, 1630, 1238 cm.$^{-1}$; $[\alpha]_D^{24}$ +78° (methanol).

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Found: C, 67.40; H, 7.88.

16α-Acetoxy-17aβ-acetoxymethyl-17aα-hydroxy-D-homoandrost-4-ene-3,17-dione (IVb). To a solution of 250 mg. of the D-homo triol IVa in 3 ml. of pyridine, was added 0.5 ml. of acetic anhydride. After standing for 17 hr. at room temperature the reaction mixture was poured into water and extracted several times with ethyl acetate. The combined extracts were washed with water, dried over magnesium sulfate, filtered, and evaporated to give an oil which crystallized on trituration with acetone–petroleum ether to yield 210 mg., m.p. 158–173°. Three crystallizations from acetone-petroleum ether gave 90 mg. of IVb; m.p. 175–177°; λ_{max} 239 mμ (ε 16,700); ν_{max} 3420, 1750, 1722, 1675, 1625, 1239 cm.$^{-1}$; $[\alpha]_D^{25}$ +49° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Found: C, 67.05; H, 7.79.

17β-Hydroxymethyl-16α,17α-isopropylidenedioxy-D-homoandrost-4-ene-3,17α-dione (Va). To a stirred slurry of 500 mg. of the D-homo triol IIIa in 60 ml. of acetone, was added 6 drops of 72% aqueous perchloric acid. Complete solution resulted immediately and the reaction mixture was allowed to stand for 16 hr. at room temperature. Water (10–20 ml.) was added followed by a slow addition of aqueous sodium bicarbonate until the mixture was neutral. Removal of the acetone under reduced pressure gave a solid which was fil-

(26) Celite is Johns-Manville's registered trade mark for diatomaceous silica products.

tered, washed with water, dissolved in acetone and crystallized from acetone–petroleum ether to give 460 mg., m.p. 208–210°. Three crystallizations from acetone-petroleum ether yielded 260 mg. of Va; m.p. 212.5–214.5°; λ_{max} 239 mμ (ε 15,700); ν_{max} 3395, 1719, 1665, 1616 cm.$^{-1}$; $[\alpha]_D^{25}$ +69° (methanol).

Anal. Calcd. for $C_{24}H_{34}O_5$ (402.51): C, 71.61; H, 8.51. Found: C, 71.59; H, 8.71.

17β-Acetoxymethyl-16α,17α-isopropylidenedioxy-D-homoandrost-4-ene-3,17a-dione (Vb). A To a solution of 90 mg. of the D-homo acetonide Va in 1.5 ml. of pyridine was added 0.2 ml. of acetic anhydride. The mixture was heated for 1 hr. on the steam bath, poured into water and the resulting solid was filtered and washed with water to give 90 mg. of Vb, m.p. 202–204°. Three crystallizations from acetone–petroleum ether raised the m.p. to 205–206°; λ_{max} 240 mμ (ε 15,700); ν_{max} 1750, 1727, 1680, 1626, 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ +81° (chloroform).

Anal. Calcd. for $C_{26}H_{36}O_6$ (444.55): C, 70.24; H, 8.16. Found: C, 70.05; H, 8.22.

B. To a solution of 165 mg. of the monoacetate IIIc in 10 ml. of acetone was added 3 drops of 72% perchloric acid and the reaction mixture was allowed to stand for 2 hr. at room temperature. Water (5 ml.) was added and the solution was neutralized with sodium bicarbonate followed by the addition of water. Filtration gave 50 mg. of solid which was recrystallized from acetone–petroleum ether to give Vb. Its infrared spectrum was identical to that of the sample prepared in *A* above.

17aβ-Hydroxymethyl-16α,17aα-isopropylidenedioxy-D-homoandrost-4-ene-3,17-dione (VI). To a solution of 100 mg. of the D-homo triol IVa in 12 ml. of acetone was added 1 drop of 72% perchloric acid and the solution was allowed to stir for 2 hr. at room temperature. Water was added followed by aqueous sodium bicarbonate until the solution was neutral. Evaporation gave a turbid solution which crystallized on scratching to afford 45 mg. of VI. Three crystallizations from acetone–petroleum ether gave 20 mg.; m.p. 203–204.5°; λ_{max} 240 mμ (ε 17,000); ν_{max} 3480, 1709, 1682, 1620 cm.$^{-1}$; $[\alpha]_D^{25}$ +82° (methanol).

Anal. Calcd. for $C_{24}H_{34}O_5$ (402.51): C, 71.61; H, 8.51. Found: C, 71.80; H, 8.65.

17β-Acetoxymethyl-16α,17α-dihydroxy-D-homoandrost-4-ene-3,17a-dione (IIIc). A solution of 0.39 g. of the acetonide acetate Vb in 15 ml. of 66% aqueous acetic acid was heated on the steam bath for 5 hr., poured into water, neutralized with sodium bicarbonate, and extracted with chloroform. The combined extracts were washed with water, dried, and evaporated to give 0.30 g. of glass which was chromatographed on 15 g. of Florisil.[27] Elution with petroleum ether–30% acetone gave appreciable amounts of oil which were combined to give 0.21 g. of glass. Ether trituration afforded 0.10 g. of IIIc; m.p. 150–190°; ν_{max} 3400, 1741, 1709, 1668, 1620 cm.$^{-1}$

All attempts to further purify this material led only to poor-looking solids which were highly solvated.

17β-Acetoxymethyl-17α-hydroxy-16α-methanesulfonyloxy-D-homoandrost-4-ene-3,17a-dione (IIId). To a solution of 2.05 g. of the monoacetate IIIc in 20 ml. of pyridine, previously cooled to 5°, was added 2 ml. of methanesulfonyl chloride. The reaction mixture was allowed to stand at 5° for 18 hr. and then poured into water and extracted with ethyl acetate. The combined extracts were washed, dried and evaporated to give 2.6 g. of oil, which was chromatographed on 100 g. of Florisil.[27] Elution with petroleum ether–25% acetone through 100% acetone afforded appreciable amounts of oil, which were combined, 1.05 g. All attempts to crystallize this material failed. An infrared spectrum indicated that the desired mesylate IIId was present in this oil (ν_{max} 1362, 1178, and 948 cm.$^{-1}$).

21-Hydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione (VII). To a stirred slurry of 250 mg. of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) in 30 ml. of acetone was added 3 drops of 72% perchloric acid. Complete solution occurred within 5 min., and the reaction mixture was allowed to stand overnight. Water (40–50 ml.) was added, and the solution was neutralized with sodium bicarbonate. The resulting solid was collected by filtration and washed with water to give 270 mg., m.p. 236–245°. Three crystallizations from acetone–petroleum ether gave material melting at 242–250°; λ_{max} 240 mμ (ε 16,500); ν_{max} 3450, 1709, 1675, 1621 cm.$^{-1}$; $[\alpha]_D^{25}$ +137° (chloroform).

Anal. Calcd. for $C_{24}H_{34}O_5$ (402.51): C, 71.61; H, 8.51. Found: C, 71.55; H, 8.58.

17-Acetoxymethyl-D-homoandrosta-4,16-diene-3,17a-dione (VIII). To a solution of 1 g. of crude monoacetate mesylate IIId in 30 ml. of acetone was added 2.5 g. of sodium iodide. The mixture was placed in a sealed tube and heated at 115° for 18 hr. The reaction mixture was cooled, the solids were removed by filtration, and washed with chloroform. The combined filtrates and washings were washed with 5% sodium thiosulfate solution and then several times with water, and evaporated to give 0.57 g. of an oil. The oil was submitted to partition chromatography on Celite[26] using the system heptane-methanol (1:1). Hold-back volumes 4 and 5 were combined and evaporated to give 0.11 g. of oil which solidified on treatment with ether. Three crystallizations from acetone-petroleum ether gave 0.035 g. of VIII; m.p. 138–139°; λ_{max} 236–237 mμ (ε 19,600); ν_{max} 1757, 1744, 1669, 1620, 1218 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.14; H, 8.38.

21-Acetoxy-16β-formyloxy-17α-hydroxypregn-4-ene-3,20-dione (Id). 21-Acetoxy-16α,17α-epoxypregn-4-ene-3,20-dione (1.0 g.) was dissolved in a mixture of 10 ml. of 98% formic acid and 0.5 ml. of sulfuric acid and allowed to stand at room temperature for 4 hr. The reaction mixture was poured into water and the resulting solid was filtered, washed well with water, and dissolved in acetone. The solution was dried, and addition of petroleum ether gave 0.41 g. of solid. Three crystallizations from acetone–petroleum ether yielded 0.16 g. of Id; m.p. 185–187°; λ_{max} 238 mμ (ε 17,700); ν_{max} 3390, 1732, 1660, 1620, 1238 cm.$^{-1}$; $[\alpha]_D^{25}$ +90.6° (chloroform).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.50): C, 66.65; H, 7.46. Found: C, 66.40; H, 7.75.

Treatment of 21-acetoxy-16β-formyloxy-17α-hydroxypregn-4-ene-3,20-dione (Id) *with potassium bicarbonate.* To a solution of 250 mg. of 21-acetoxy-16β-formyloxy-17α-hydroxypregn-4-ene-3,20-dione (Id) in 20 ml. of methanol was added 2 ml. of a 5% solution of potassium bicarbonate in 1:1 methanol-water. The reaction mixture was allowed to stand at room temperature in a nitrogen atmosphere for 1 hr. and was then neutralized with acetic acid. Removal of the methanol *in vacuo* at room temperature gave an oil which was dissolved in methylene chloride, dried over magnesium sulfate and evaporated. This gave 260 mg. of oil which was partitioned on Celite[26] with the system methylene chloride–ethylene glycol (1:1). Evaporation of the latter part of hold-back volume 1 plus part of 2 gave an oil which was added to water and extracted with ethyl acetate. The combined extracts were dried and evaporated to give an oil which crystallized from acetone–petroleum ether to yield 70 mg. of solid, m.p. 148–170°. The infrared spectrum of this material was almost identical to that of the pure sample of 16β-acetoxy-17α,21-dihydroxypregn-4-ene-3,20-dione (Ic) prepared below.

The crude 16β-monoacetate Ic was dissolved in 3 ml. of pyridine and treated with 0.3 ml. of acetic anhydride overnight at room temperature. The reaction mixture was treated with methanol and evaporated to give an oil which crystallized on scratching with ether to yield 25 mg., m.p. 162–164°. The infrared spectrum was identical to that of an authentic sample of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia).

(27) Florisil is the Floridin Co.'s registered trademark for a synthetic magnesium silicate.

Treatment of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia) *with perchloric acid. A.* A solution of 1.0 g. of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia) in 30 ml. of 0.27*N* perchloric acid in methanol was allowed to stand at room temperature for 17 hr. and then poured into water. The aqueous mixture was extracted with ethyl acetate and the combined extracts were washed with water until neutral, dried over sodium sulfate, and evaporated to give 800 mg. of oil. The oil was submitted to partition chromatography on a Celite[26] column with the system 7:1:2—methylene chloride–ethyl acetate–ethylene glycol. The latter part of hold-back volume 2 plus part of 3 were evaporated to give an oil which was added to water. The mixure was extracted with ethyl acetate, and the extract was dried and evaporated to give an oil which crystallized from methanol-ether. Two further crystallizations gave 50 mg. of 16β,17α,21-trihydroxypregn-4-ene 3,20-dione (Ib); m.p. 196–201°[28]; λ_{max} 240 mμ (ε 16,300); ν_{max} 3350, 1718, 1653, 1610 cm.$^{-1}$; $[\alpha]_D^{25}$ + 109° (methanol).

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 69.33; H, 8.77.

The latter part of hold-back volume 1 was evaporated to give an oil which was extracted with ethyl acetate. The combined extracts were dried and evaporated to give an oil which crystallized from acetone–petroleum ether to yield 110 mg.; m.p. 196–200°. Two further crystallizations gave 70 mg. of an unknown compound; m.p. 210–212.5°; λ_{max} 240 mμ (ε 16,800); ν_{max} 3420, 1709, 1665, 1618 cm.$^{-1}$; $[\alpha]_D^{25}$ + 54° (methanol).

Anal. Calcd. for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34. Found: C, 69.39; H, 8.55.

The diacetate of this unknown compound prepared in the usual manner had m.p. 189–190.5°; ν_{max} 3490, 1748, 1675, 1625, and 1230 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Calcd. for $C_{25}H_{34}O_7 \cdot {}^1/_2\ H_2O$ (455.53): C, 65.91; H, 7.74. Found: C, 66.22; H, 7.91.

B. In another run, 4.15 g. of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ib) gave, after partition chromatography, the two compounds described above plus a third compound contained in the early part of hold-back volume 1. This was evaporated and on addition of water gave 470 mg. of solid. Three crystallizations from acetone–petroleum ether gave 180 mg., m.p. 198–200°. The infrared spectrum of this material was identical to that of 16β-acetoxy-17α,21-dihydroxypregn-4-ene-3,20-dione (Ic) prepared in the hydrochloric acid hydrolysis experiment.

C. In another run on 5 g. of Ib, there was isolated 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa), 0.22 g. 16α,17aα - dihydroxy - 17aβ - hydroxymethyl - D - homoandrost-4-ene-3,17-dione (IVa), 0.13 g.; 16α,17α-dihydroxy-17β - hydroxymethyl - D - homoandrost - 4 - ene - 3,17a - dione (IIIa), 0.33 g.; and 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib), 0.43 g.

Treatment of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (I) *with hydrochloric acid. A.* To a solution of 1.0 g. of 16β,21 - diacetoxy - 17α - hydroxypregn - 4 - ene - 3,20 - dione (Ia) in 25 ml. of methanol and 4 ml. of water, cooled to 10°, was added 2 ml. of concd. hydrochloric acid dropwise. The reaction was allowed to stand at room temperature overnight, poured into water and worked up as in the case of the perchloric acid hydrolysis followed by chromatography on Celite.[26] This gave after crystallization from acetone-petroleum ether 110 mg. of 16β-acetoxy-17α,21-dihydroxypregn-4-ene-3,20-dione (Ic)[29]; m.p. 189–192°; λ_{max} 240 mμ (ε 17,000); ν_{max} 3480, 1740, 1718, 1680, 1625, and 1239 cm.$^{-1}$; $[\alpha]_D^{25}$ +111° (methanol).

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.97. Found: C, 68.08; H, 8.08.

(28) Ref. 21 gave m.p. 190–191°; λ_{max} 241 mμ (ε 16,300); $[\alpha]_D^{21}$ +118° (chloroform) for Ib.

(29) Ref. 20a gave m.p. 188–190°; $[\alpha]_D^{21}$ +104° (chloroform) for Ic.

There was also isolated 120 mg. of 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib), m.p. 185–191°. This was reacetylated to the diacetate Ia and was identical to authentic material in melting point and infrared spectrum.

B. To a solution of 300 mg. of the 16β,21-diacetate Ia in 30 ml. of methanol was added 3 ml. of concd. hydrochloric acid. After refluxing for 1 hr., there was added 1.5 g. of sodium acetate and the mixture was evaporated to 5 ml. Addition of water gave a gum which was extracted with ethyl acetate. The combined extracts were washed with sodium bicarbonate solution and then with water until neutral. Evaporation of the solution gave a semisolid which was submitted to partition chromatography on a Celite[26] column. Evaporation of hold-back volume 2 and addition of water gave 10 mg. of solid, m.p. 180–195° whose infrared spectrum was identical to the D-homo triol IIIa.

Treatment of 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib) *with potassium hydroxide.* To a solution of 500 mg. of 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib) in 30 ml. of methanol was added 200 mg. of potassium hydroxide in 5 ml. of methanol. The reaction mixture was allowed to stand at room temperature for 1 hr. in a nitrogen atmosphere. Neutralization with acetic acid followed by evaporation to a small volume gave 260 mg. of a poor-looking solid. Treatment with 20 ml. of boiling methanol gave 60 mg. of insoluble material, m.p. 238–241°. This compound had an infrared spectrum identical to that of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) and a mixed melting point determination showed no depression.

The soluble methanol fraction was evaporated and partition-chromatographed on a Celite[26] column using the system 7:2:1:—methylene chloride–ethylene glycol–ethyl acetate. Hold-back volume 2 was evaporated and crystallized from methanol-ether to yield 30 mg., m.p. 190–201°. Its infrared spectrum was identical to that of the D-homo triol IIIa.

Part of hold-back volume 1 was evaporated and on addition of water furnished an additional 30 mg. of IIa, m.p. 238–241°.

Treatment of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) *with ferric chloride-dimethylformamide.* To a solution of 200 mg. of 16α,17α,21-trihydroxy-pregn-4-ene-3,20-dione (IIa) in 10 ml. of dimethylformamide was added 0.3 ml. of 3% aqueous ferric chloride solution. The reaction mixture was heated for 30 min. on the steam bath when 50 ml. of water was added. The turbid mixture was extracted with ethyl acetate and the extract was dried and evaporated until only dimethylformamide remained. Ether was added to give crystals which were separated by filtration and washed with ether to yield 90 mg., m.p. 218–222°. One crystallization from acetone-petroleum ether gave 45 mg., m.p. 226–229°. Its infrared spectrum was identical to that of the D-homo triol IVa prepared previously.

16β,21-Diacetoxy-3-ethylenedioxy-17α-hydroxypregn-5-en-20-one (IX). To a solution of 1.0 g. of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia) in 30 ml. of 2-methyl-2-ethyl-1,3-dioxolane was added 30 mg. of *p*-toluenesulfonic acid monohydrate. The mixture was heated to boiling and the temperature maintained so as to distill 15 ml. of the dioxolane through a Vigreux column over a 3-hr. period. The solution was then cooled and benzene was added. The benzene solution was washed with sodium bicarbonate solution and then with water until neutral. After being dried, the solution was evaporated to give a solid which on treatment with acetone–petroleum ether yielded 550 mg. of IX. Three crystallizations from acetone-petroleum ether gave 310 mg.; m.p. 232–234°; ν_{max} 3490, 1740, 1725 (shoulder), 1243 cm.$^{-1}$; $[\alpha]_D^{25}$ −15° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_8$ (490.57): C, 66.10; H, 7.81. Found: C, 66.01; H, 7.95.

16β,21-Diacetoxy-3-ethylenedioxypregn-5-ene-17α,20β-diol (Xa). To a solution of 350 mg. of 16β,21-diacetoxy-3-ethylenedioxy-17α-hydroxypregn-5-en-20-one (IX) in 9 ml. of dimethylformamide was added a solution of 90 mg. of

sodium borohydride in 2.5 ml. of water. The solution gelled almost immediately whereupon an additional 8 ml. of dimethylformamide was added in order to bring about complete solution. The reaction mixture was allowed to stand for 1 hr. at room temperature, and was then neutralized with acetic acid and poured into water to give a gel. This mixture was extracted with ethyl acetate and the extract was washed and evaporated to give a solid which resisted all attempts at purification, giving only a gel with a variety of solvents. Evaporation of the gel to dryness *in vacuo* gave a residue which amounted to 300 mg.

16β,20β,21-Triacetoxy-3-ethylenedioxypregn-5-en-17α-ol (Xb). *A.* To a solution of 300 mg. of the crude 16,21-diacetate Xa in 5 ml. of pyridine was added 0.5 ml. of acetic anhydride. The reaction mixture was heated for 1 hr. on the steam bath and poured into water to yield a semisolid which was separated by filtration, washed with water, dissolved in acetone, and the solution was evaporated to give a solid. An ether slurry gave 110 mg. of Xb, m.p. 244–254°. Three crystallizations from acetone-petroleum ether raised the m.p. to 284–289°; ν_{max} 3490, 1749, 1255 cm.$^{-1}$; $[\alpha]_D^{25}$ −33° (chloroform).

Anal. Calcd. for $C_{29}H_{42}O_9$ (534.63): C, 65.15; H, 7.92. Found: C, 65.23; H, 8.14.

B. To a solution of 120 mg. of crude tetrol-3-ketal Xc in 7 ml. of pyridine was added 1 ml. of acetic anhydride. The solution was heated for 1 hr. on the steam bath, poured into water to give 90 mg., 255–270°. Three crystallizations from acetone-petroleum ether gave 20 mg., m.p. 285–289°. The infrared spectrum was identical to that of the sample prepared in *A*.

3-Ethylenedioxypregn-5-ene-16β,17α,20β,21-tetrol (Xc). To a solution of 0.77 g. of 16β,20β,21-triacetoxy-3-ethylenedioxypregn-5-en-17α-ol (Xb) in 145 ml. of methanol, previously flushed with nitrogen, was added a solution of 0.52 g. of potassium hydroxide in 20 ml. of methanol. After standing for 1 hr. at room temperature, the reaction mixture was neutralized with acetic acid and evaporated until about one half the volume remained. The resulting solid (530 mg.) was collected by filtration and washed with water. Three crystallizations from methanol gave 0.19 g. of Xc; m.p. 286–289°; ν_{max} 3430 and 1100 cm.$^{-1}$; $[\alpha]_D^{25}$ −18.5° (pyridine).

Anal. Calcd. for $C_{23}H_{36}O_6$ (408.52): C, 67.62; H, 8.88. Found: C, 67.37; H, 8.51.

16α,21-Diacetoxy-3-ethylenedioxy-17α-hydroxypregn-5-en-20-one (XI). *A.* To a solution of 2.6 g. of 16α,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (IIb) in 100 ml. of 2-methyl-2-ethyl-1,3-dioxolane was added 100 mg. of *p*-toluenesulfonic acid monohydrate. The mixture was heated to boiling and the temperature maintained so as to distil *ca.* 50 ml. of the dioxolane through a Vigreux column over a 3-hr. period. The reaction mixture was cooled, benzene was added and the benzene solution was washed with sodium bicarbonate solution and water until neutral. After being dried, the solution was evaporated to give 2.9 g. of oil. Treatment with ether afforded 0.30 g. of XI, m.p. 182–188°. Three crystallizations from acetone-petroleum ether yielded 0.075 g., m.p. 264–269°; ν_{max} 3450, 1742, 1723 (shoulder), 1238 cm.$^{-1}$; $[\alpha]_D^{25}$ − 43.5° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_8$ (490.57): C, 66.10; H, 7.81. Found: C, 65.86; H, 8.20.

B. To a solution of 0.50 g. of the 16β,21-diacetoxy-3-ketal IX, in 25 ml. of methanol, previously flushed with nitrogen, was added 0.16 g. of potassium hydroxide in 5 ml. of methanol. After standing for 1 hr., the mixture was neutralized with acetic acid and evaporated at 35°. The resulting solid (300 mg.) had a melting range of 158–280°. The material was dissolved in 10 ml. of pyridine, treated with 1 ml. of acetic anhydride, and heated for 1 hr. on the steam bath. Addition of water gave a solid which was separated and recrystallized from acetone-petroleum ether to give 35 mg., m.p. 262–266°. The infrared spectrum was identical to that of the sample in *A* above.

21-Acetoxy-16α,17α-(2′-butylidenedioxy)pregn-4-ene-3,20-dione (XIIa). *A.* To a solution of 200 mg. of 16α,17α-(2′ - butylidenedioxy) - 21 - hydroxypregn - 4 - ene - 3,20-dione (XIIb) in 3 ml. of pyridine was added 0.3 ml. of acetic anhydride. The reaction mixture was heated on the steam bath for 1 hr., cooled and water was added. The resulting solid was filtered and washed with water to yield 220 mg. of XIIa, m.p. 185–187.5°. Two crystallizations from acetone-petroleum ether gave 140 mg.; m.p. 185–187.5°; λ_{max} 240 mμ (ε 17,200); ν_{max} 1760, 1730, 1682, 1620 cm.$^{-1}$; $[\alpha]_D^{25}$ +112° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_6$ (458.57): C, 70.71; H, 8.35. Found: C, 70.89; H, 8.47.

B. The mother liquor from the ketal reaction on 16α,21-diacetoxy - 17α - hydroxypregn - 4 - ene - 3,20 - dione (IIa) was evaporated to give 2.6 g. of oil which was chromatographed on 100 g. of Florisil.[27] Elution with petroleum ether–6% acetone provided 0.35 g. of crystalline material. Three crystallizations from acetone–petroleum ether gave 0.18 g. of XIIa, m.p. 189–192°. The infrared spectrum of this material was identical to that of *A* above.

16α,17α-(2′-Butylidenedioxy)-21-hydroxypregn-4-ene-3,20-dione (XIIb). To a solution of 0.40 g. of 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) in 50 ml. of methyl ethyl ketone was added 6 drops of 72% perchloric acid. The reaction mixture was stirred for 3 hr. at room temperature, (solution was complete in 2 hr.) water was added and the solution was neutralized with sodium bicarbonate solution and concentrated at 35–40° until crystals formed. The solid was filtered and washed with water to give 0.45 g. of XIIb, m.p. 184–188°. Two crystallizations from acetone-petroleum either 0.34 g., m.p. 186–188.5°; λ_{max} 241 mμ (ε 16,100); ν_{max} 3480, 1709, 1680, 1620 cm.$^{-1}$; $[\alpha]_D^{25}$ + 131° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71. Found: C, 71.60; H, 8.94.

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